Ipertensione Arteriosa: una diagnosi e una terapia sempre “ facili” ?

Alberto Morganti
U.O. Medicina Generale e Centro Ipertensione Arteriosa
Ospedale San Giuseppe, Università di Milano

Corso Ecocardiochirurgia
Milano, 20-21 Maggio 2013

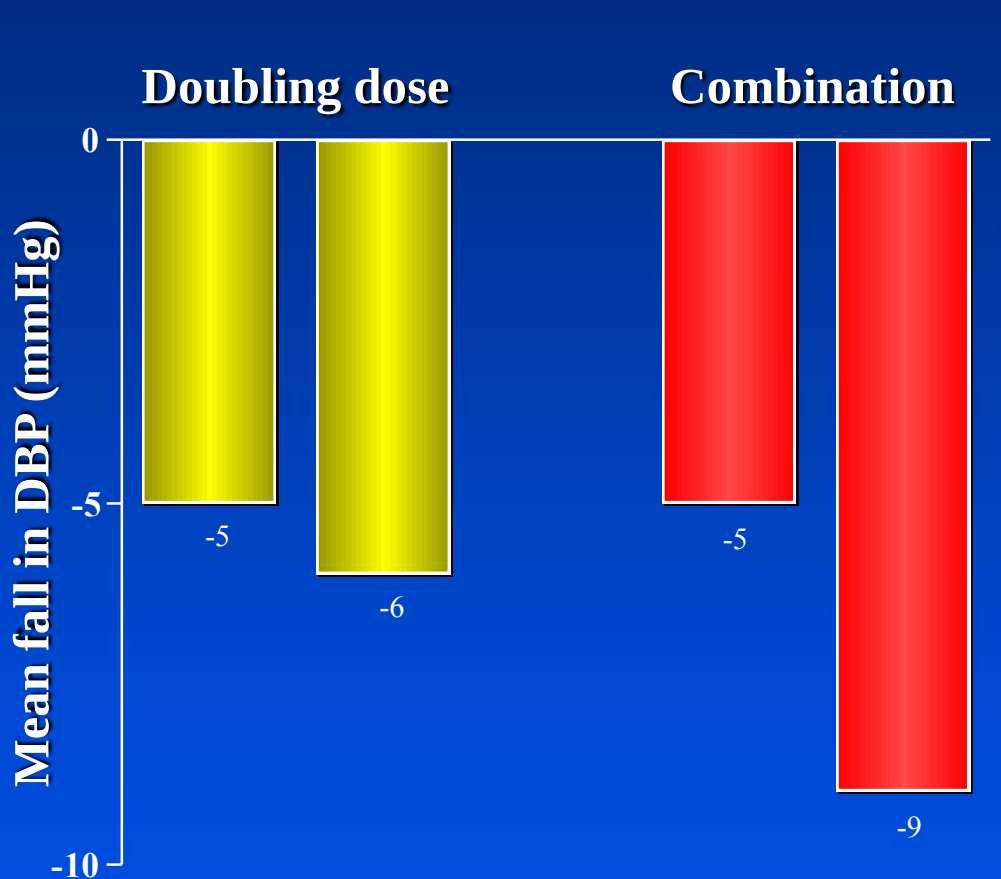
Ipertensione Arteriosa:
una diagnosi e una terapia sempre “facili” ?

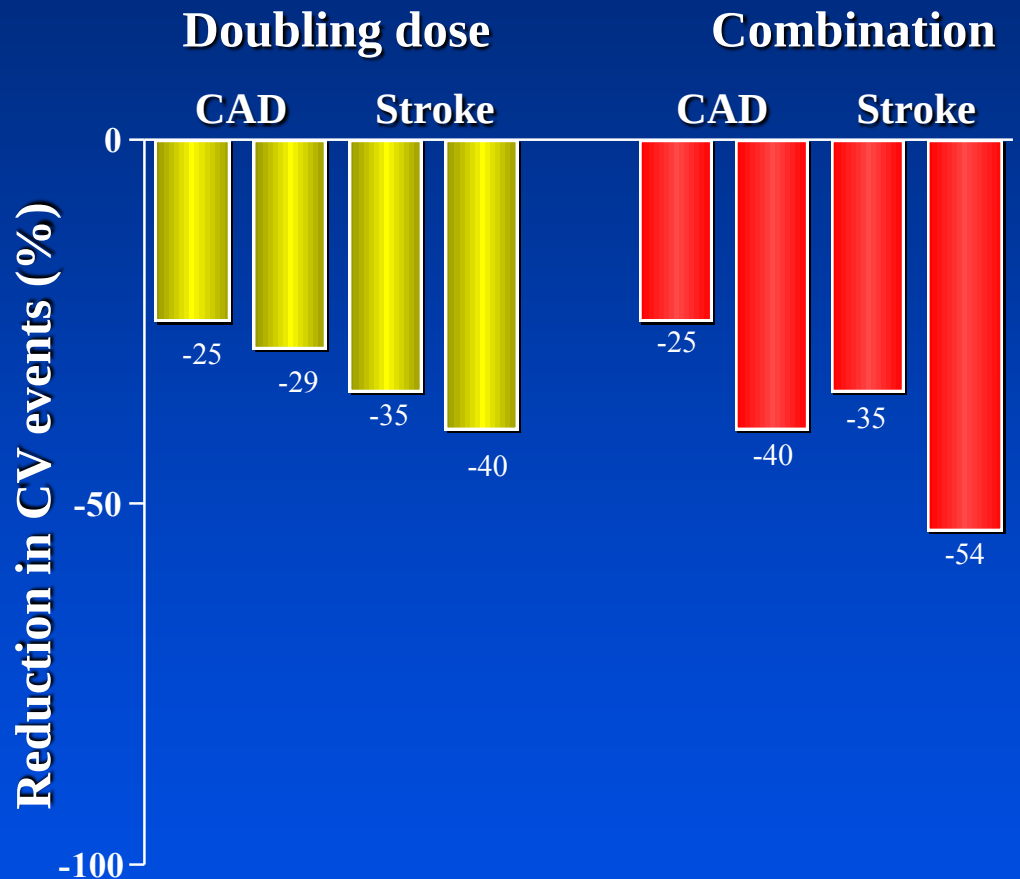
Which drugs should be used for treatment of hypertension ?

Any two

Citation from an eminent US Cardiologist 1980 circa

Effects of Doubling Dose of a Single Drug vs. Combining Two Drugs on Diastolic Blood Pressure and Cardiovascular Event Reduction



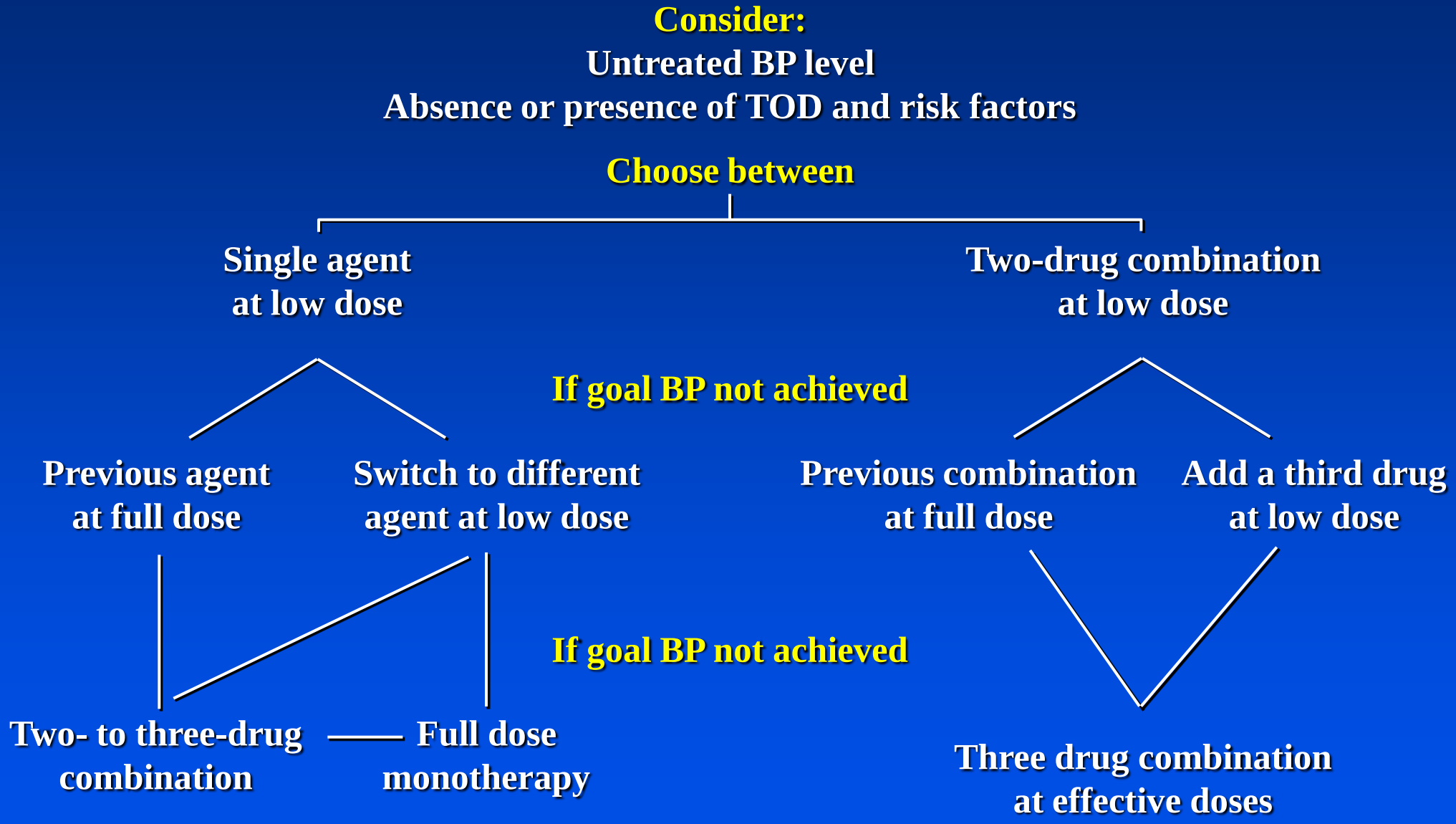


Doubling dose of single drug | Combination of two drugs low dose (any class)

Data from 42 trials (n = 10.968)

Wald SD et al., Am J Med 2009; 22: 290-300

How to Select the Antihypertensive Treatment



2003 ESH-ESC Guidelines for Management of Arterial Hypertension, J Hypertens 2003; 21: 1001-1053

Advantages of combination treatment

- Greater antiHT efficacy due to multiple mechanisms of action
- Lower incidence of side effects due to lower doses
- Increased patient compliance (particularly with fixed combination)
- Faster reaching of blood pressure target (particularly important in high risk patients)

Criteri Farmacologici per l'Associazione di Farmaci Antipertensivi

1. Associare farmaci con lo stesso profilo farmacocinetico in termini di tempo di picco e di durata d'azione
2. Associare farmaci che hanno meccanismi d'azione diversi, ma complementari tra loro
3. L'efficacia antipertensiva dell'associazione deve essere superiore all'efficacia di ciascun singolo componente (effetto additivo o di potenziamento)
4. L'associazione deve minimizzare gli effetti umorali indesiderati
5. L'associazione deve minimizzare gli effetti collaterali indesiderati

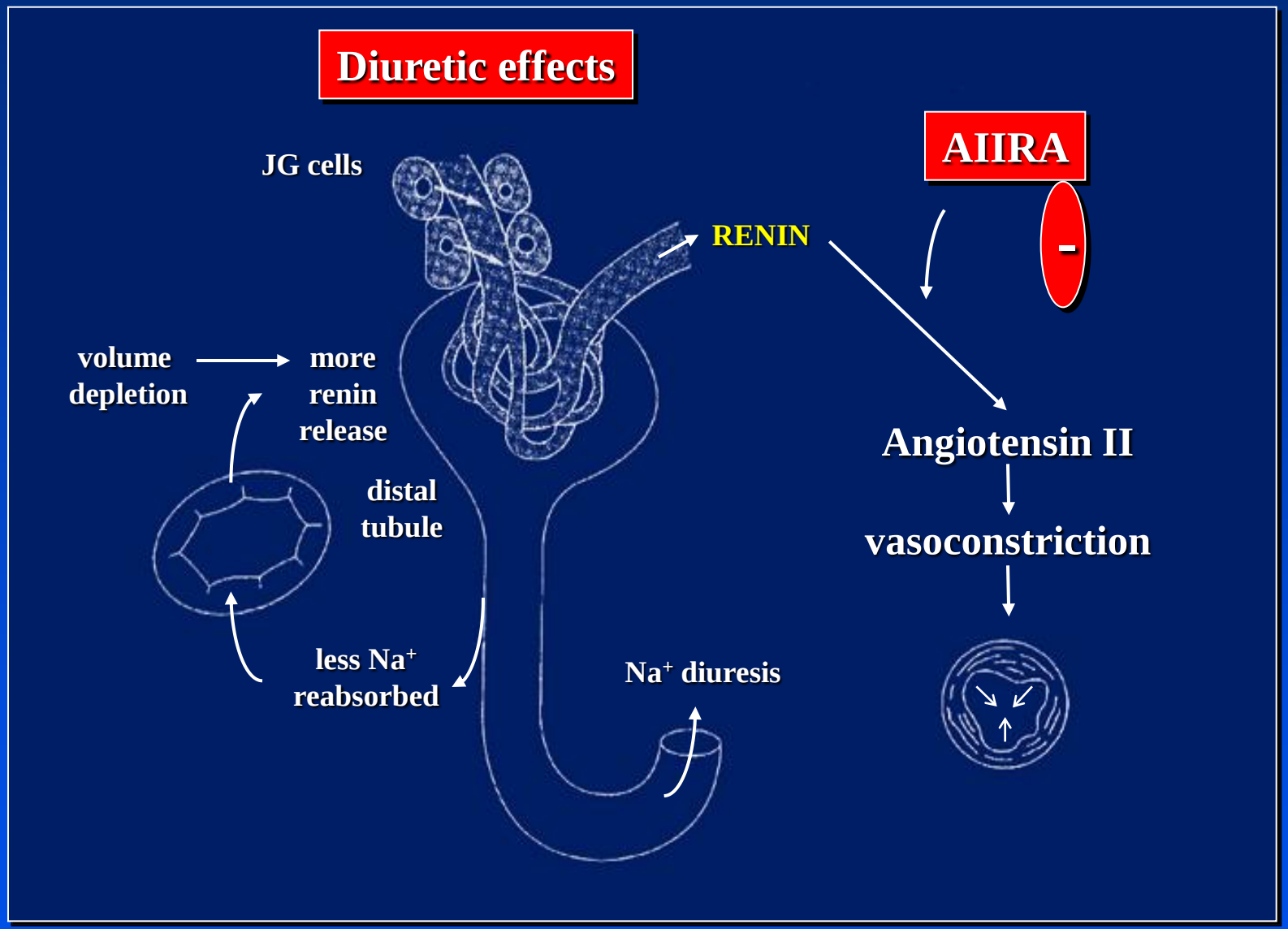
Associazioni Preformate tra Farmaci Antipertensivi: le Scelte Razionali

Combinazioni farmacologiche efficaci

- Beta bloccante + diuretico
- Beta bloccante + calcioantagonista
- Beta bloccante + alfa bloccante
- ACE inibitore + calcioantagonista
- ACE inibitore + diuretico
- ARB + diuretico

Linee Guida OMS/ISH 1999

Rationale for Combination of AII Antagonists with Diuretics



J Hypertens 2001

Meccanismi Natriuretici dei Calcio-antagonisti

- Aumento del flusso renale plasmatico (RPF)
- Vasodilatazione arteriola afferente
- Aumento del filtrato glomerulare (GFR)
- Diminuzione del riassorbimento tubulare
- Modulazione fattori vasoattivi / natriuretici (ANP, BK, NO)
- Antagonismo recettori aldosterone

↑ Diuresi, Natriuresi → → Stimolazione RAAS

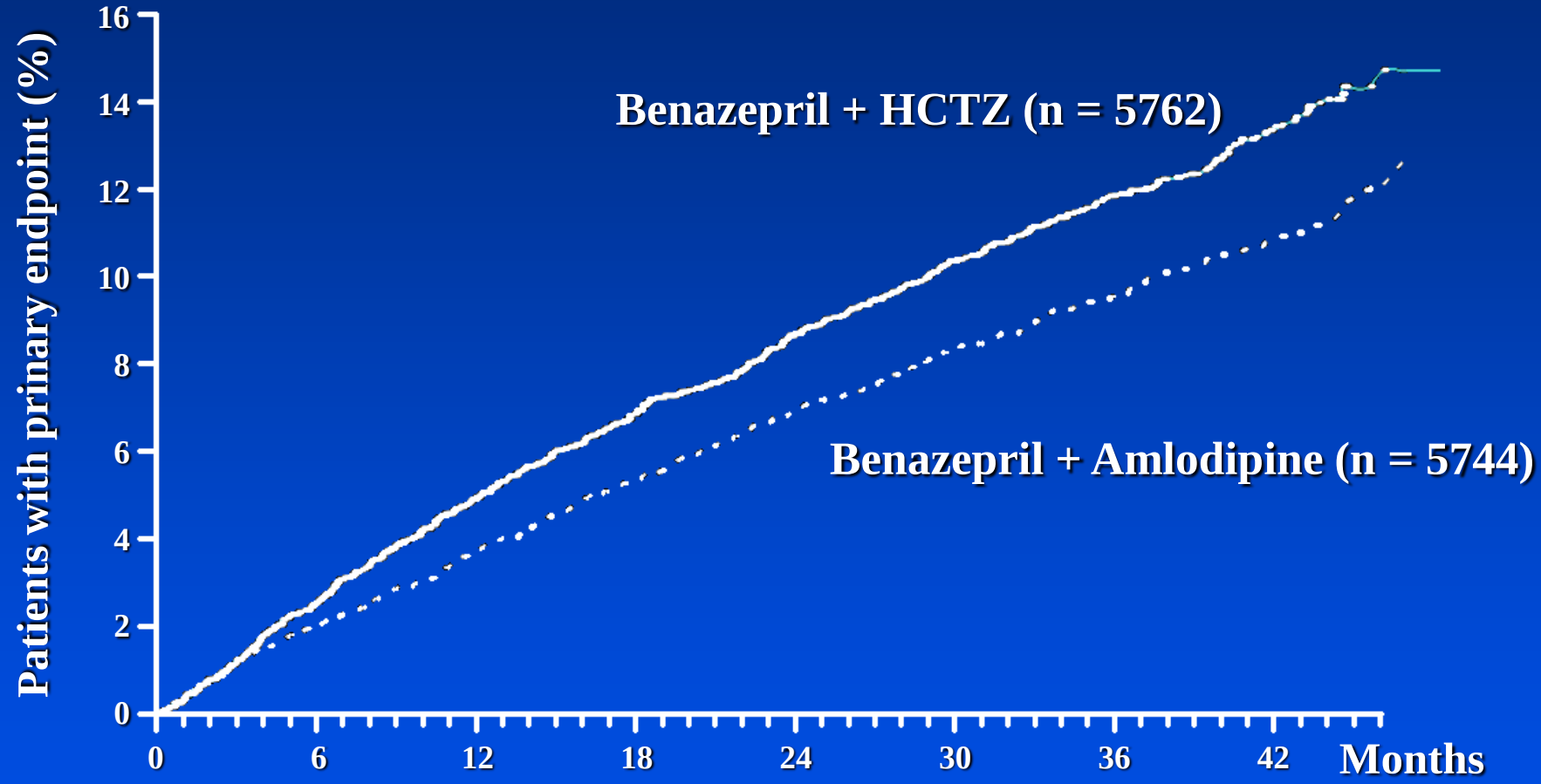
Preferred Indications of Calcium Antagonists, ACE-inhibitors and ARBs as First-line Antihypertensive Therapy

	CA-antagonists	ACE-inhibitors	ARBs
Subclinical organ damage			
Left ventricular hypertrophy	+	+	+
Asymptomatic atherosclerosis	+	+	
Microalbuminuria		+	+
Renal dysfunction		+	+
Clinical events			
Previous stroke	+	+	+
Previous MI		+	+
Angina pectoris	+		
Heart failure		+	+
Atrial fibrillation			
Recurrent		+	+
Permanent			
Peripheral artery disease	+		
Renal failure / proteinuria		+	+
Condition			
Isolated systolic hypertension	+		
Metabolic syndrome	+	+	+
Diabetes mellitus		+	+
Pregnancy	+		
Blacks	+		

2422 Mo

Mancia G et al., J Hypertens 2007; 25: 1105-1187

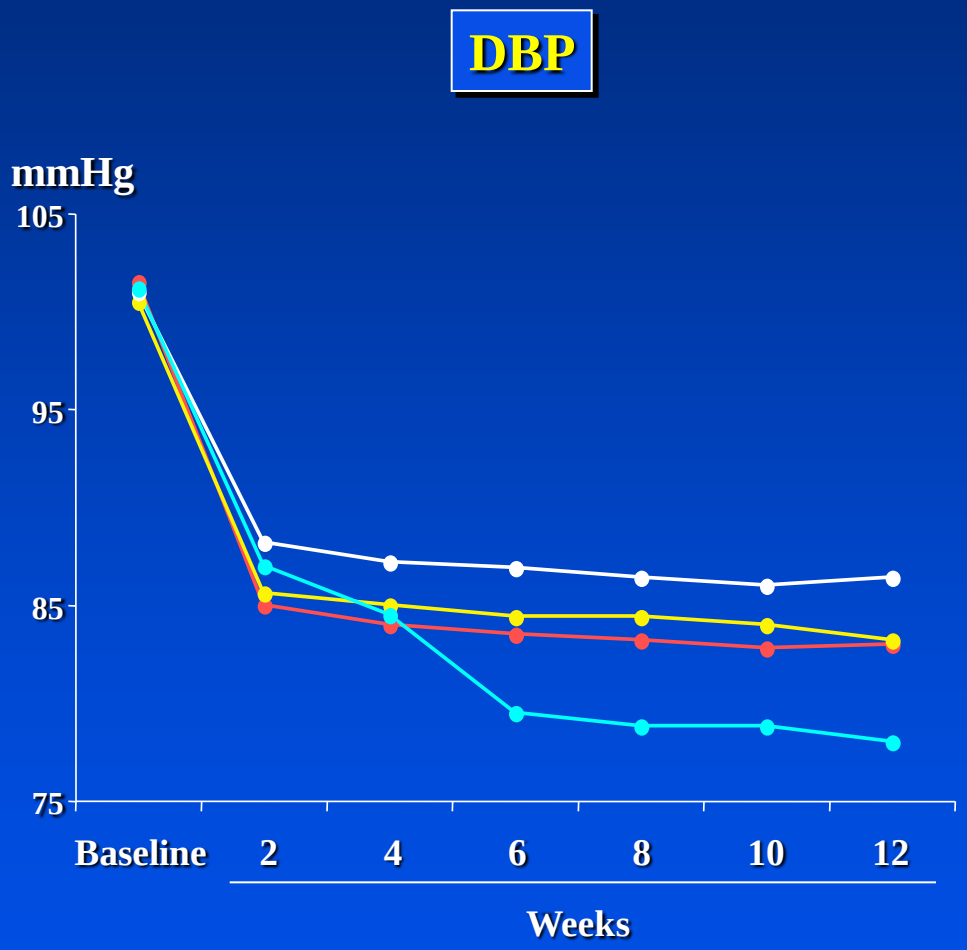
Time to First Primary Composite End Point in ACCOMPLISH Study

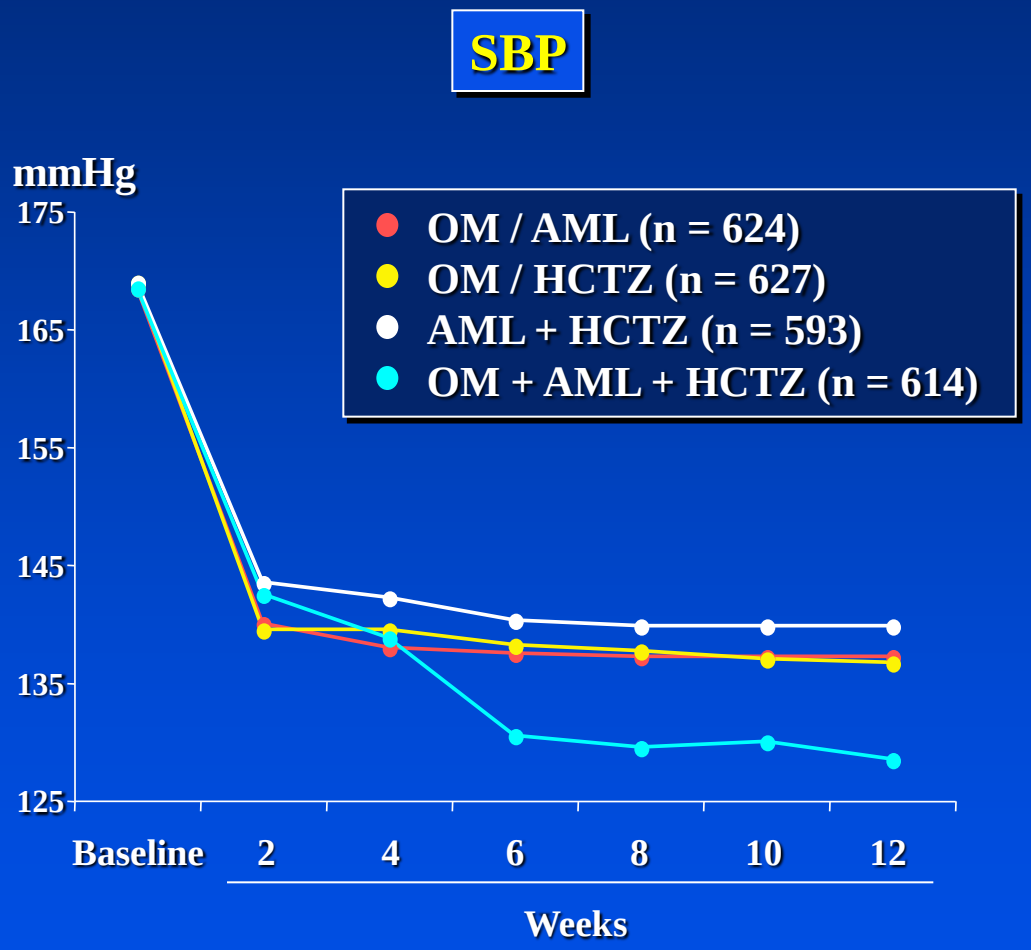


No. at Risk							
Benazepril plus amlodipine	5512	5317	5141	4959	4739	2826	1447
Benazepril plus hydrochlorothiazide	5483	5274	5082	4892	4655	2749	1390

Jamerson K et al., New Engl J Med 2008; 359: 2417-2428

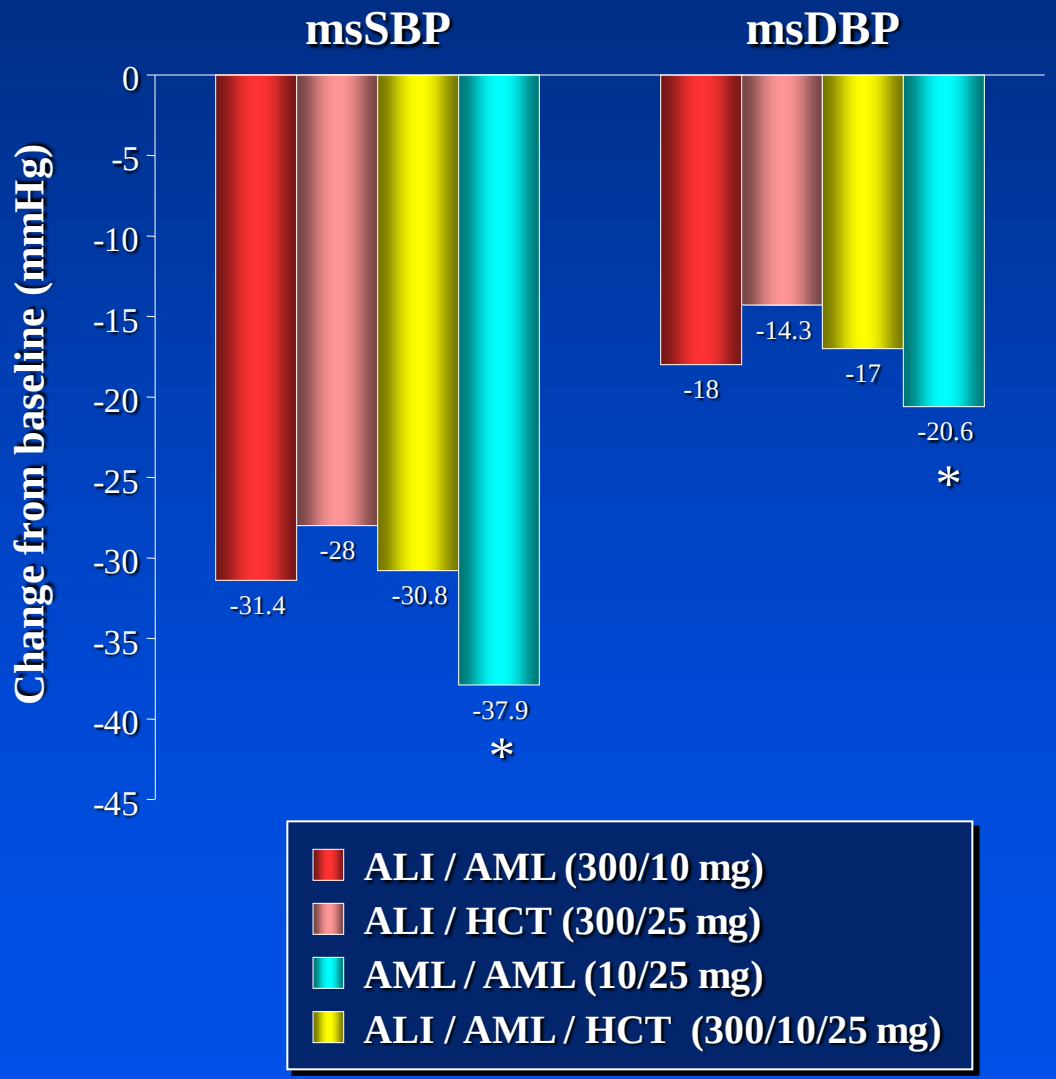
DBP and SBP over time with dual combination and triple combination treatment

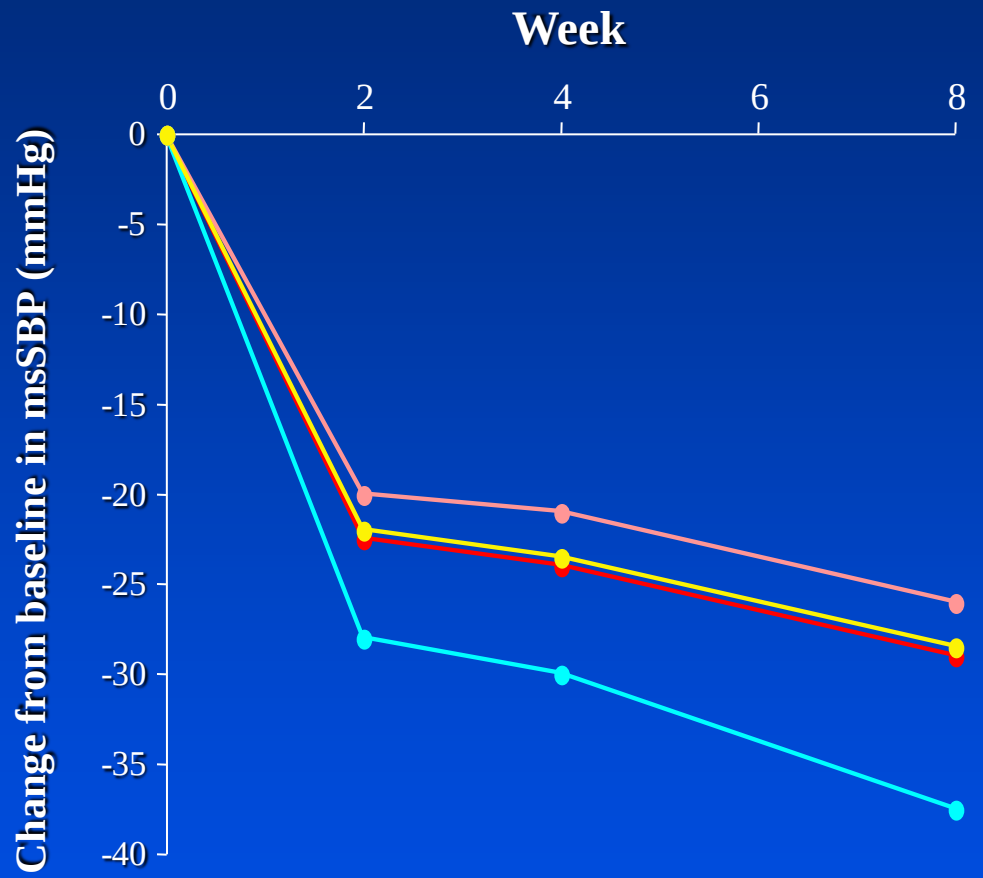




Oparil S et al., Clinical Therapeutics 2010; 32: 1252-1259

Blood pressure lowering effect of aliskiren in double and triple combination





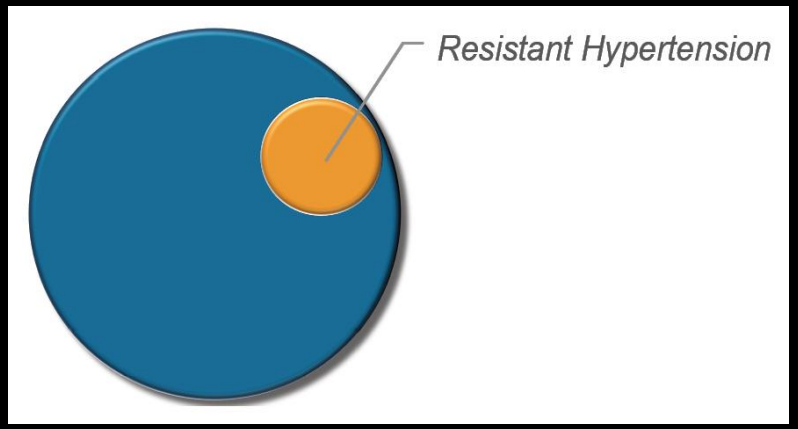
2796 Mo

Lacourcière Y et al., J Hypertens 2012; 30: 2047-2055

Resistant Hypertension

Resistant Hypertension is defined as a failure to achieve goal BP (<140/90 mmHg for the overall population and < 130/80 mmHg for those with diabetes mellitus or chronic kidney disease) when a patient adheres to maximum tolerated doses of 3 antihypertensive drugs including a diuretic.

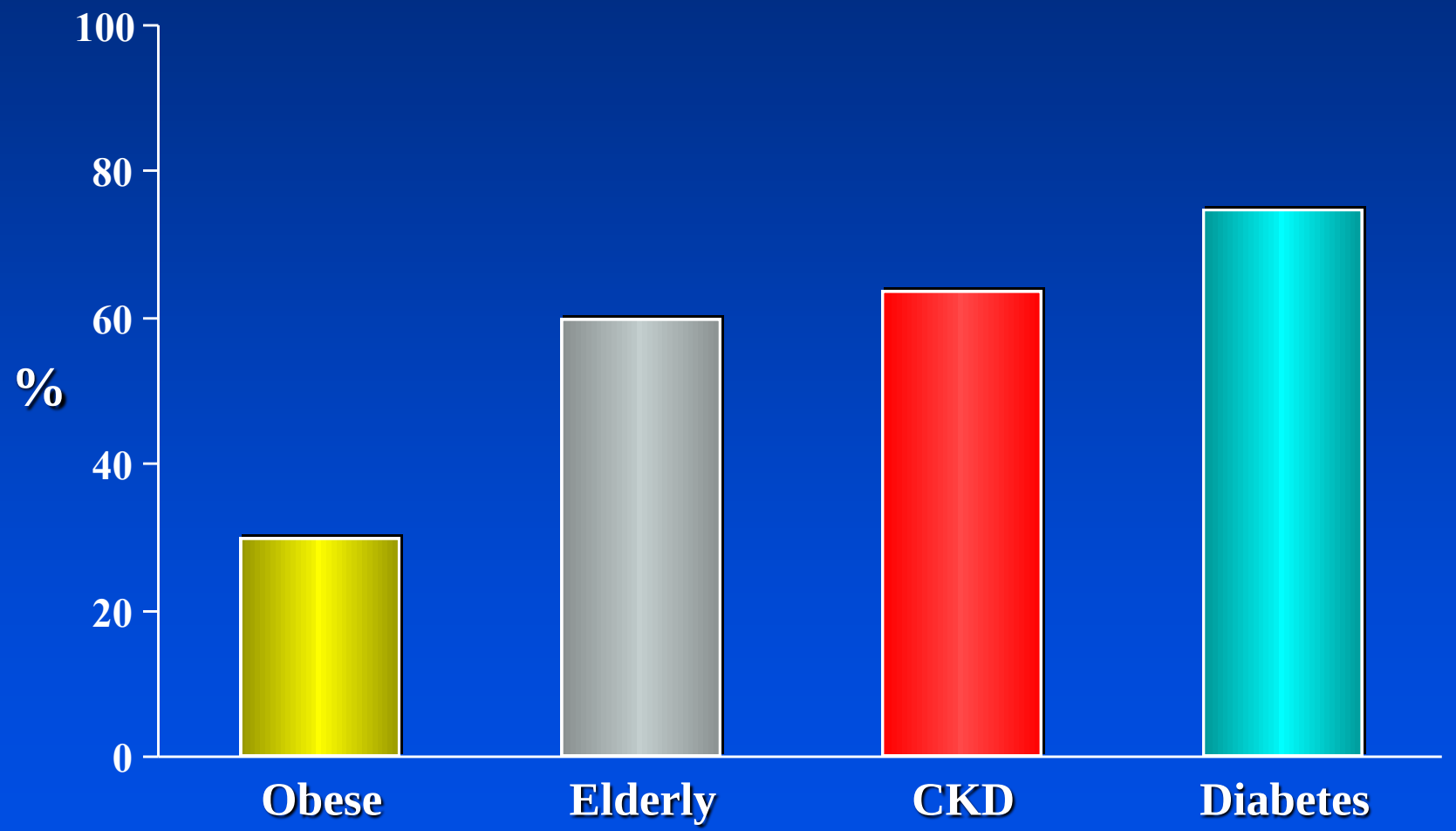
Chobanian AV, et al. *Hypertension*. 2003;42:1206-1252.



The prevalence of resistant hypertension is unknown. Cross-sectional studies suggest that it includes approximately 10% to 15% of the general hypertensive population. Patient with resistant hypertension are at incresed cardiovascular risk compared with patients with more easily controlled hypertension.

Acelajado MC, et al. *The Journal of Clinical Hypertension*. 2012;14:7-12.

Prevalence of Resistant Hypertension in Subgroup of Patients



Calhoun DA et al., Circulation 2008; 117: e510-e526

Secondary Causes of Resistant Hypertension

Common

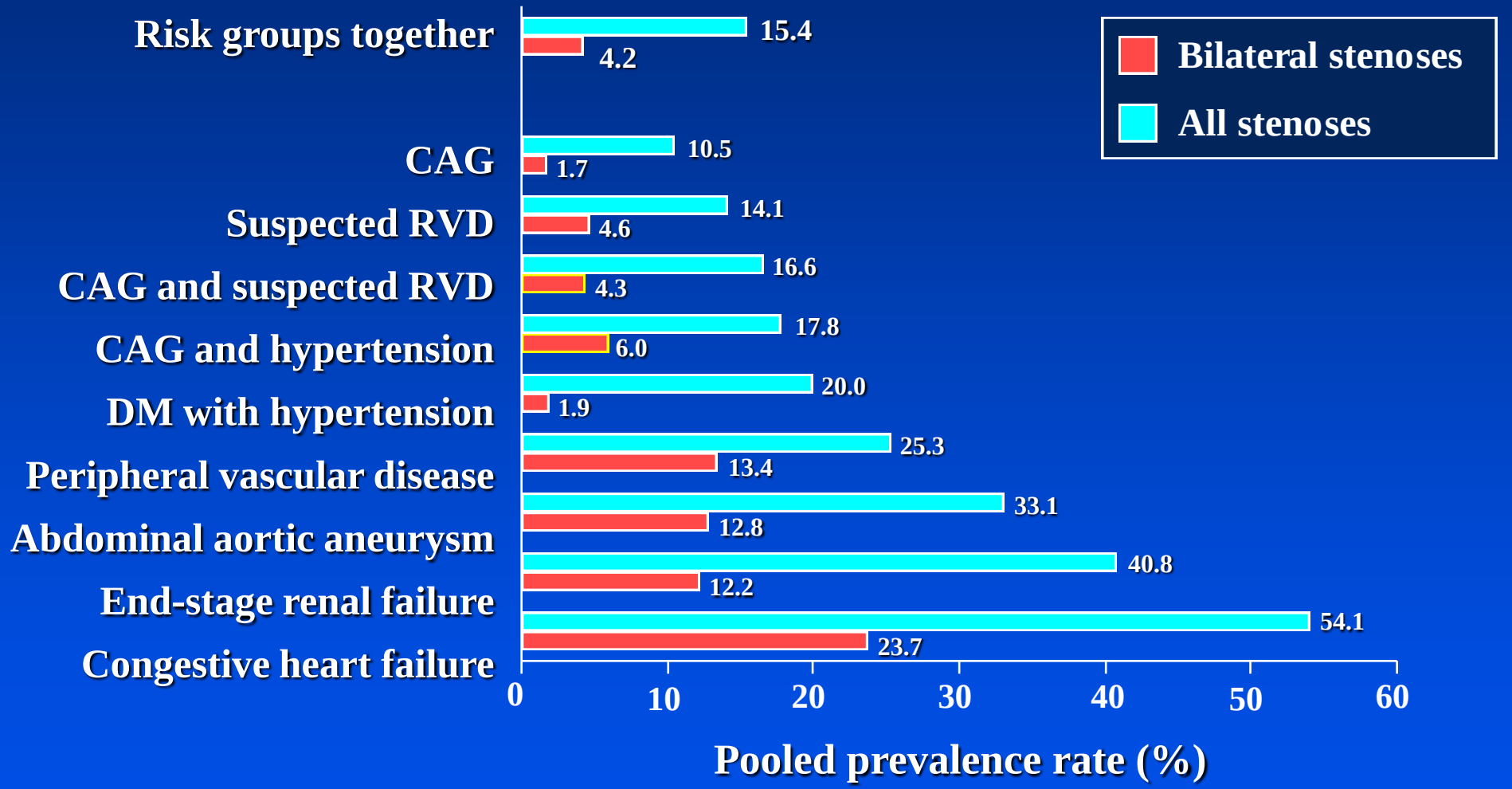
- **Obstructive sleep apnea**
- **Renal parenchymal disease**
- **Primary aldosteronism**
- **Renal artery stenosis**

Secondary Causes of Resistant Hypertension

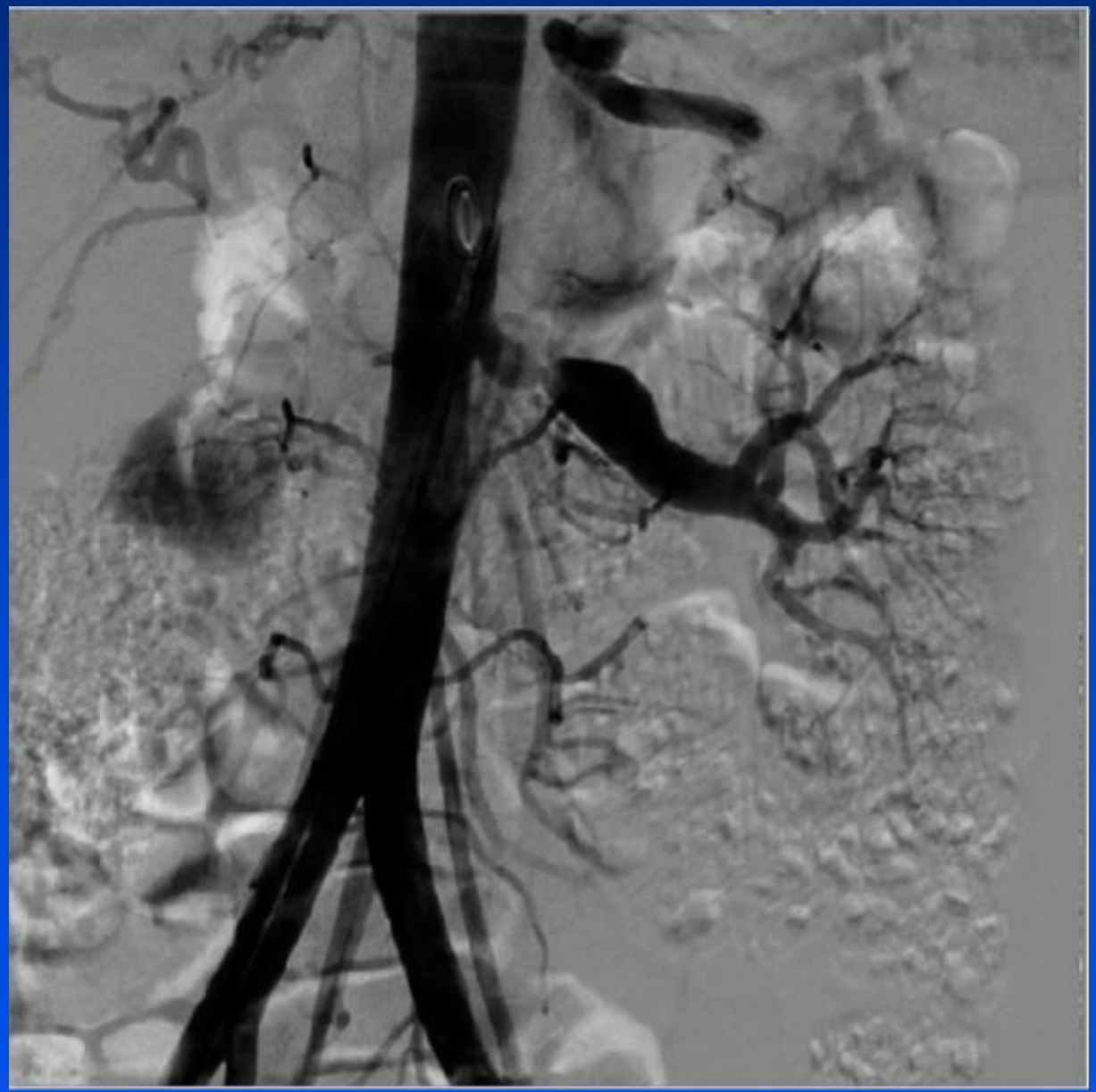
Uncommon

- Pheochromocytoma
- Cushing's disease
- Hyperparathyroidism
- Aortic coarctation
- Intracranial tumor

Pooled Prevalence Rates of Unilateral and Bilateral RAS in Risk Group Categories



de Mast Q and Bentler JJ, J Hypertens 2009, in press



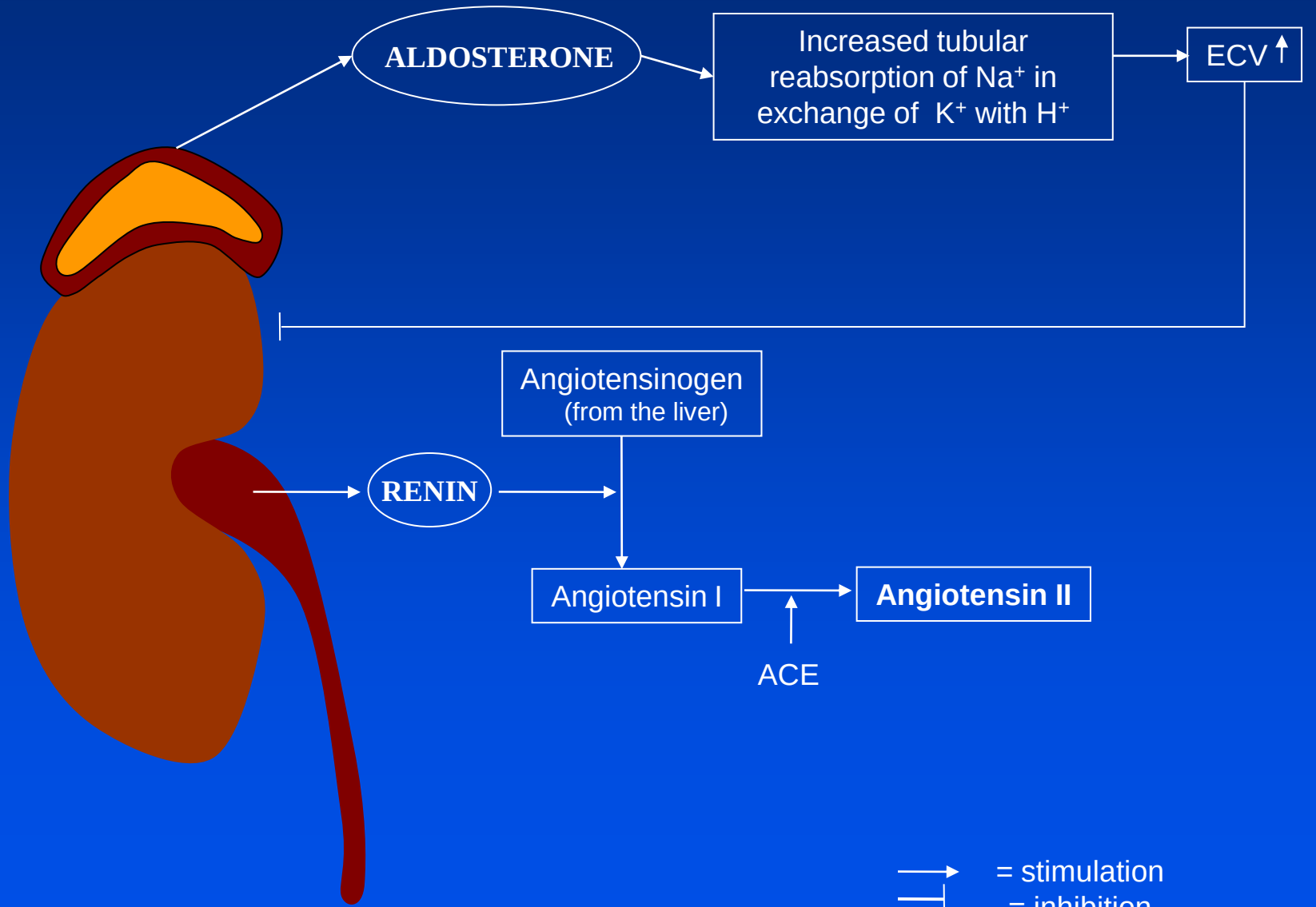
2729 Mo

Effects of PTRA on a patient with severe renal artery stenosis

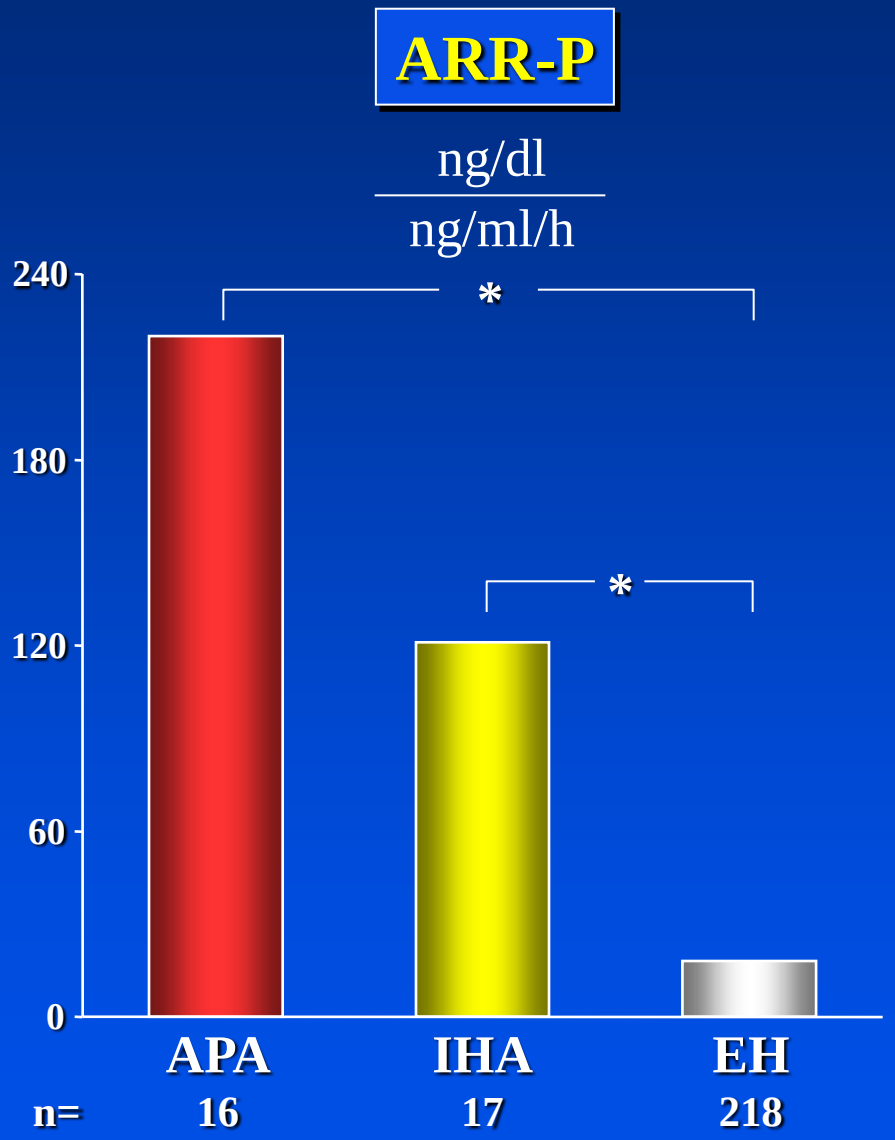
	BP (mmHg)	ABPM (24h) (mmHg)	Renin (μU/ml)	Aldo (pg/ml)	Terapia
Pre-PTRA	150/110	138/98	206	201	Amlodipine 10mg/die
5 days post-PTRA	130/90	-	17	146	-
30 days post-PTRA	130/80	128/89	12	-	-

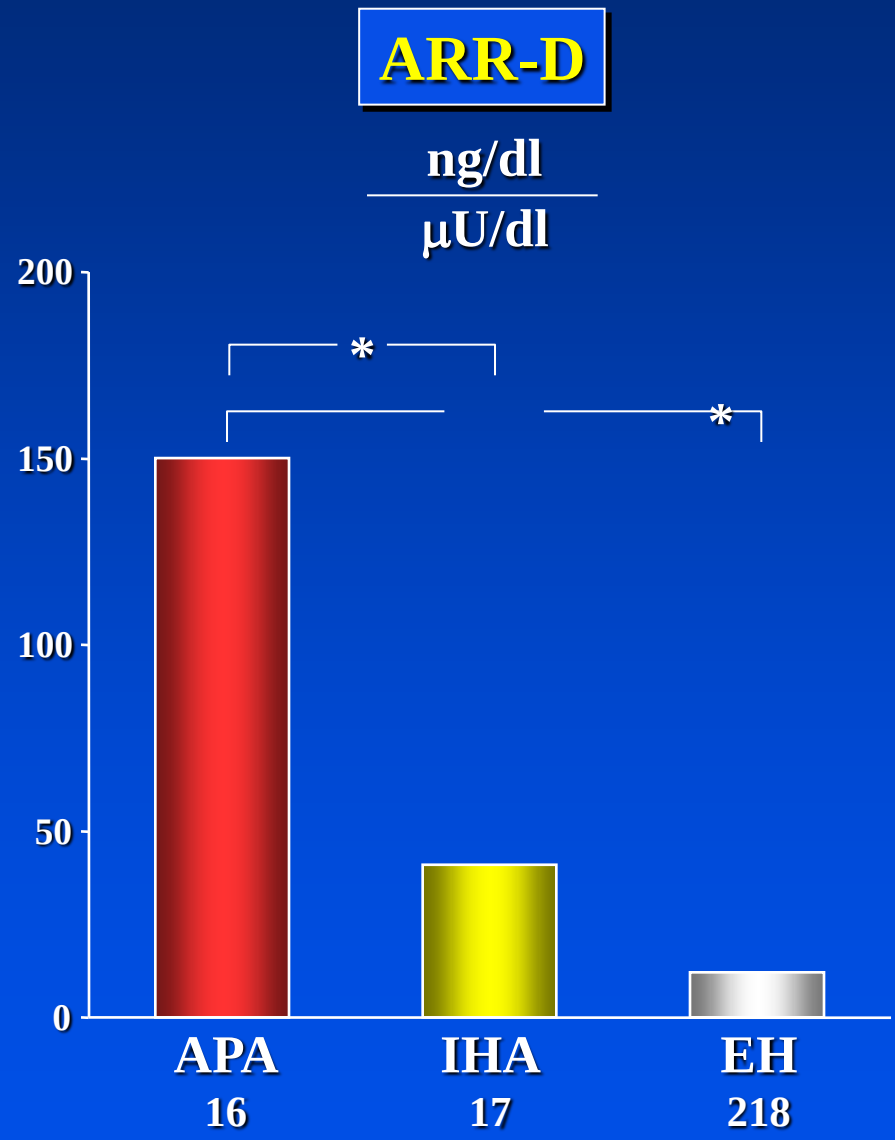
Bilateral Adrenal Tumor : TAC Imaging

RAAS (renin-angiotensin-aldosterone-system)



Comparison of ARRs calculated with PRA and DRA in patients with APA, IHA and EH





Rossi GP et al., J Hypertens 2010; 28: 1892-1899

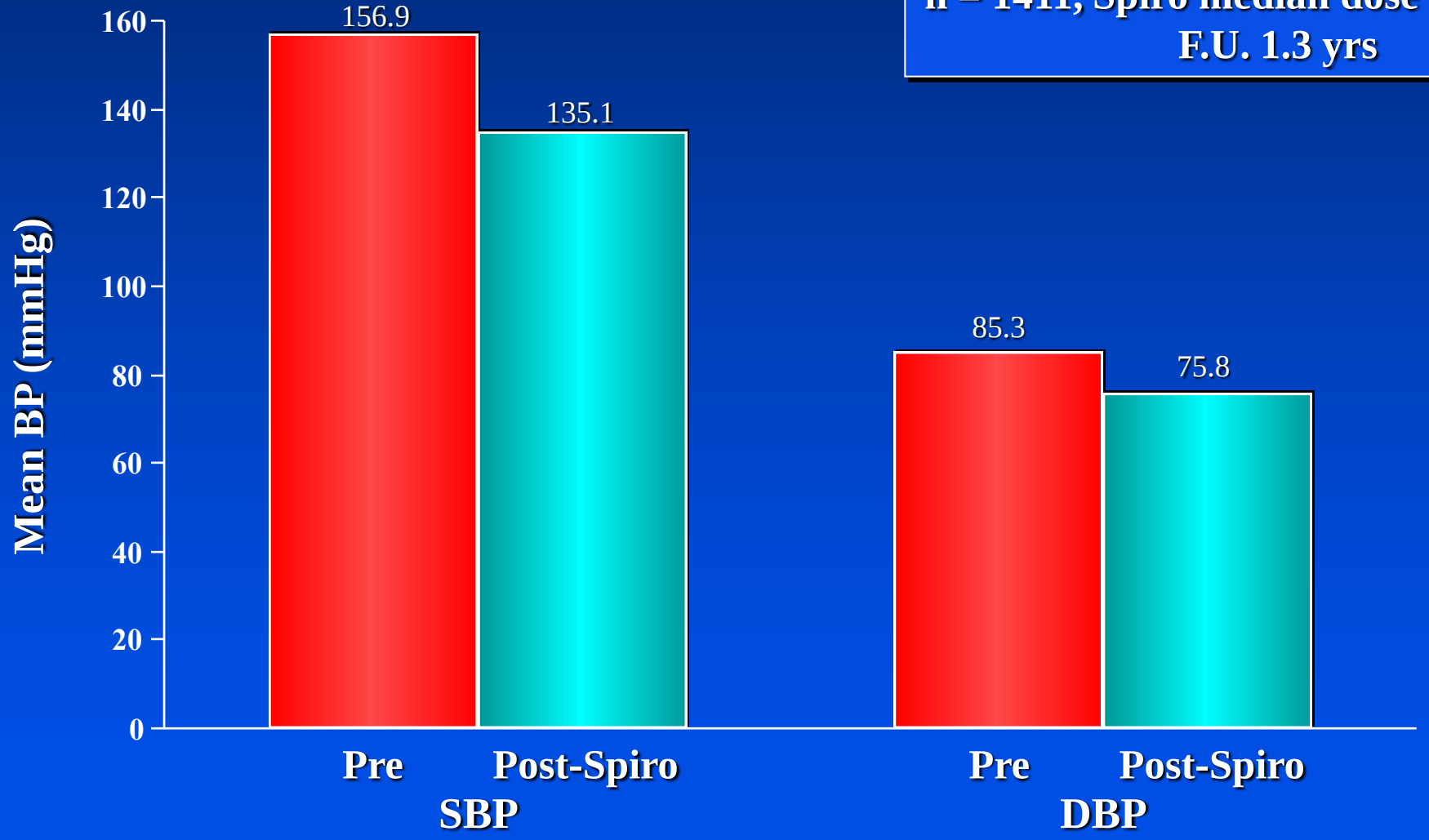
Association between resistant hypertension and low-renin / high aldosterone profile

Characteristic	Patients with resistant hypertension (n = 279)	Controls (n = 53)
Clinic SBP/DBP (mmHg)	146/86	125/79
No. of BP medications	4.1 *	0.5
Potassium (mEq/l)	3.9 *	4.3
Plasma aldosterone (mg/dl)	13.0 *	8.4
Plasma renin activity (ng/ml.h)	2.3 *	3.8
Plasma ARR	22 *	6

Gaddam KK et al., Arch Interm Med 2008; 168: 1159-1164

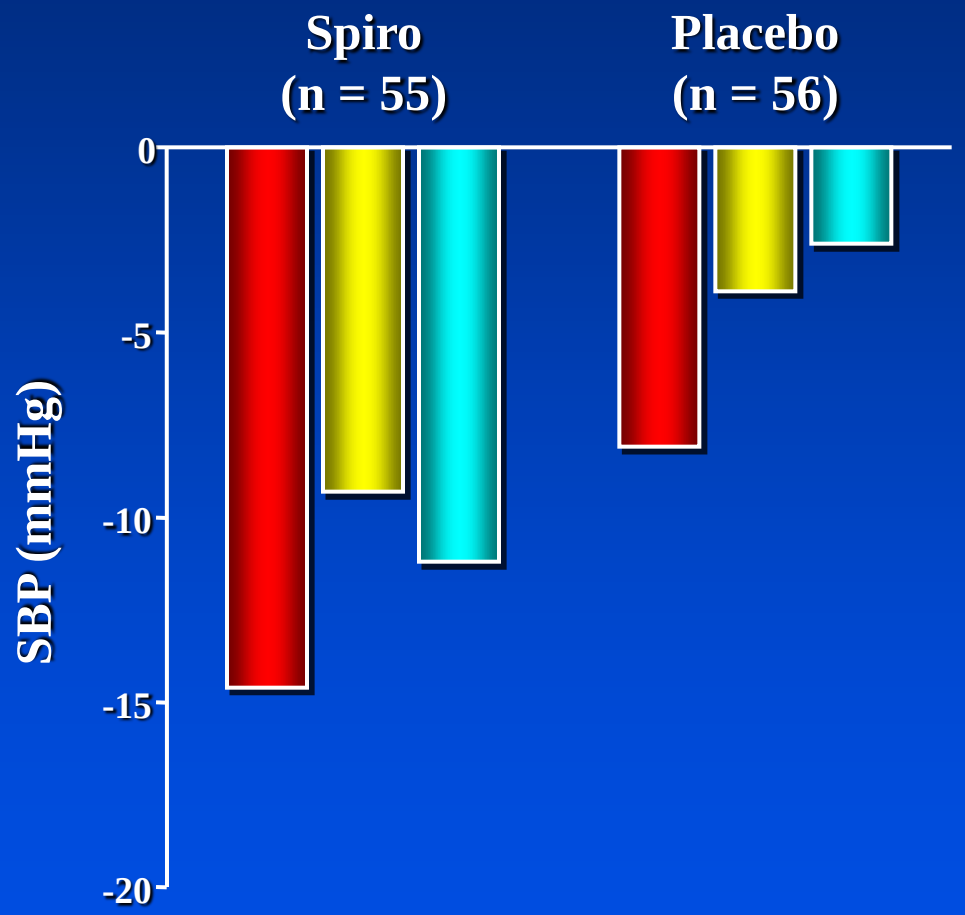
Mean BP Before and During Spironolactone Treatment in Patients with Resistant Hypertension (ASCOT trial)

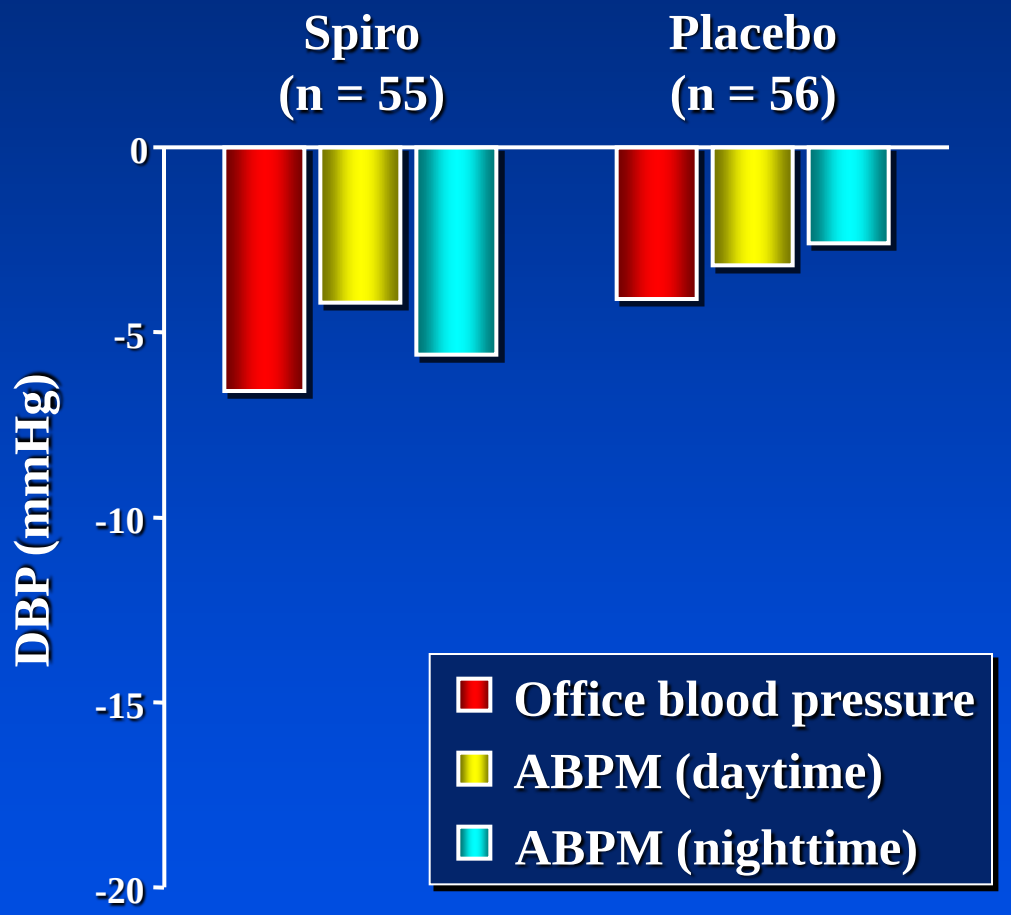
n = 1411, Spiro median dose 25 mg/day, F.U. 1.3 yrs



Chapman N et al., Hypertension 2007; 49: 839-845

Effects of spironolactone addition on BP in patients with resistant hypertension - The ASPIRANT Trial



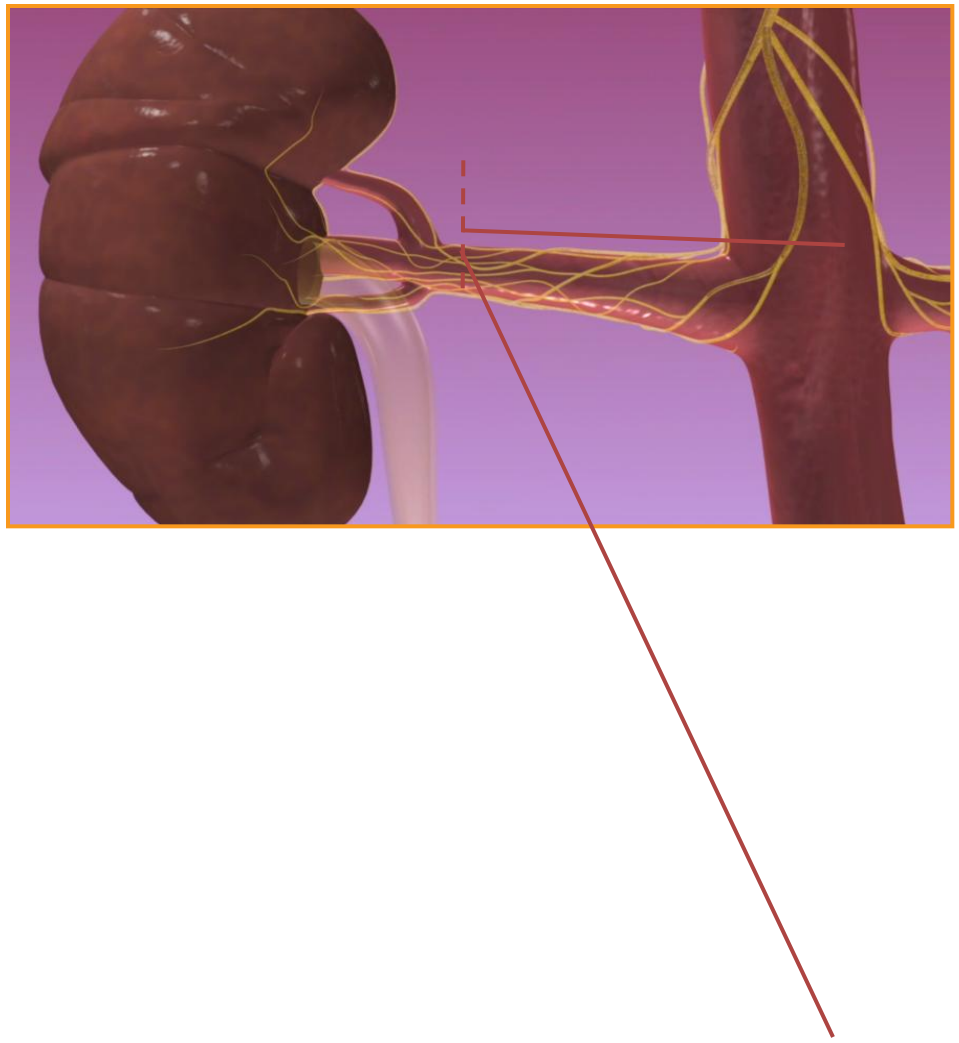


Spironolactone addition: 25 mg/day
Follow-up: 9 weeks

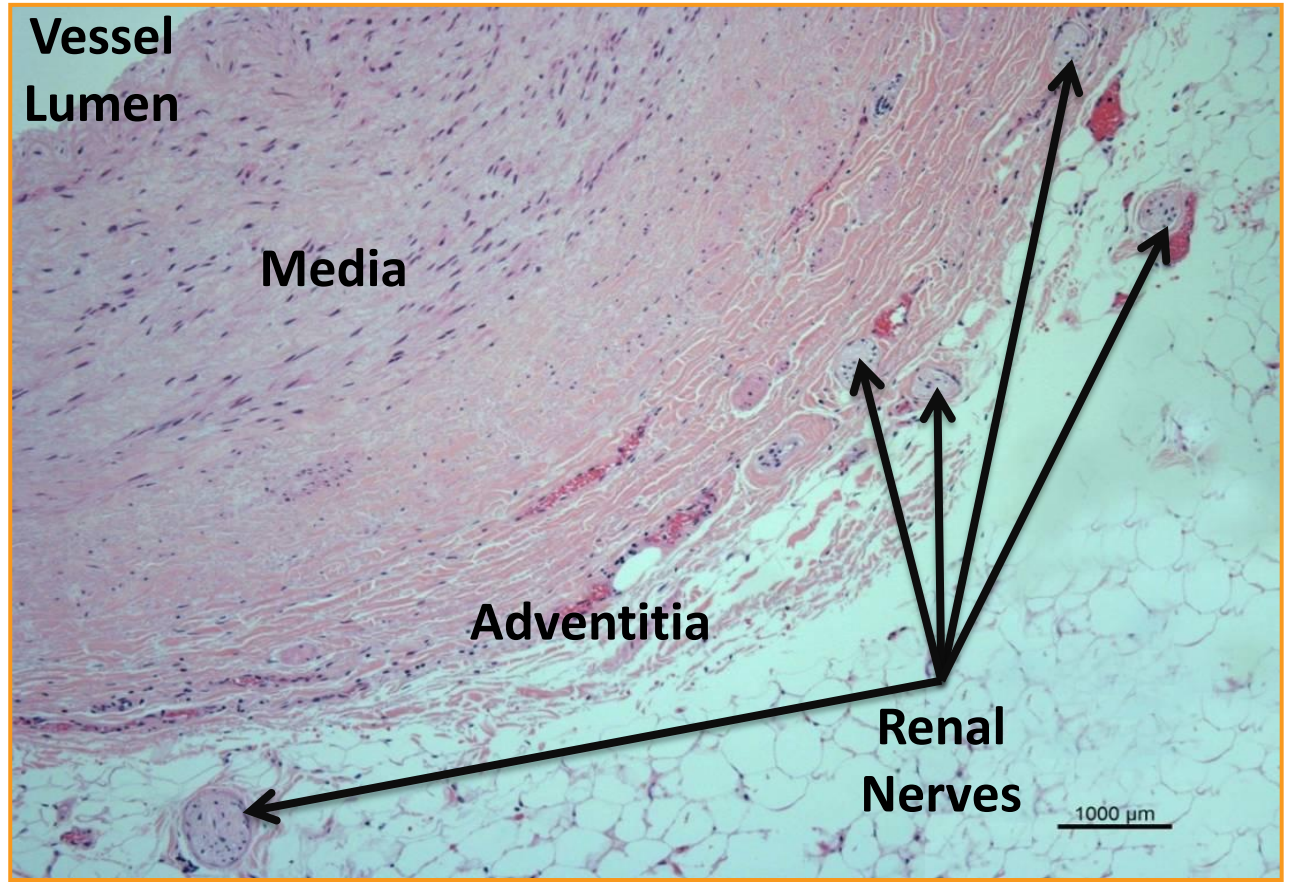
2494 Mo

Vaclavik J et al., Hypertesion online May 2011

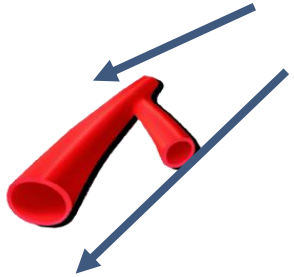
Targeting Renal Nerves

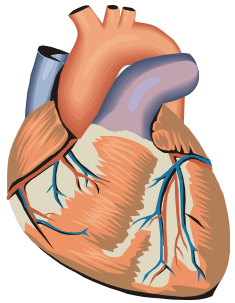


- Nerves arise from T10-L2
- The nerves arborize around the artery and primarily lie within the adventitia



Renal Sympathetic Afferent Nerves:
Kidney as Origin of Central Sympathetic Drive





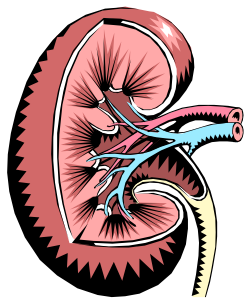
Vasoconstriction
Atherosclerosis

Insulin Resistance

Sleep Disturbances

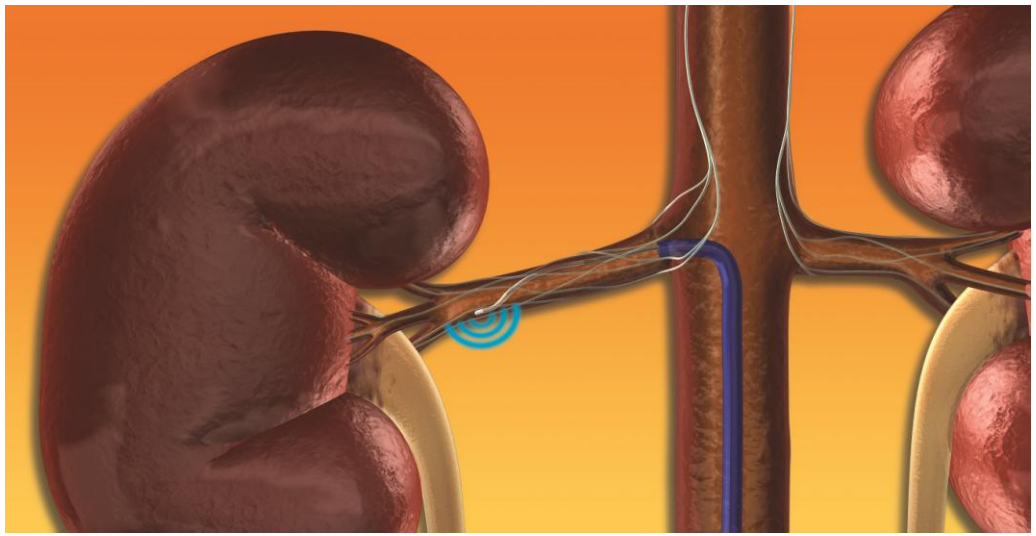
Renal Afferent Nerves

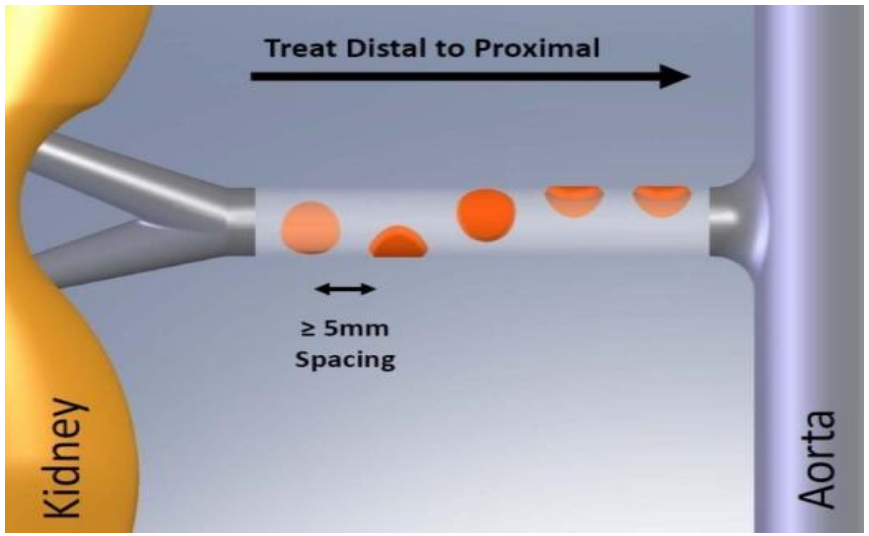
Hypertrophy
Arrhythmia
Oxygen Consumption



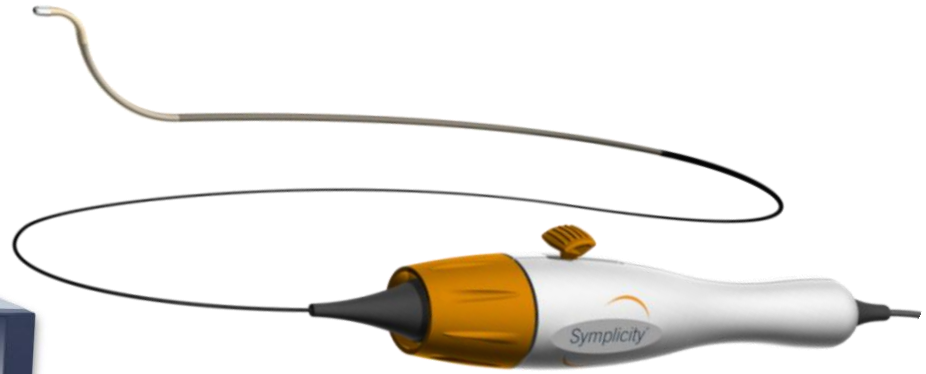
↑ Renin Release → RAAS activation
↑ Sodium Retention
↓ Renal Blood Flow

Renal Nerve Anatomy Allows a Catheter-Based Approach





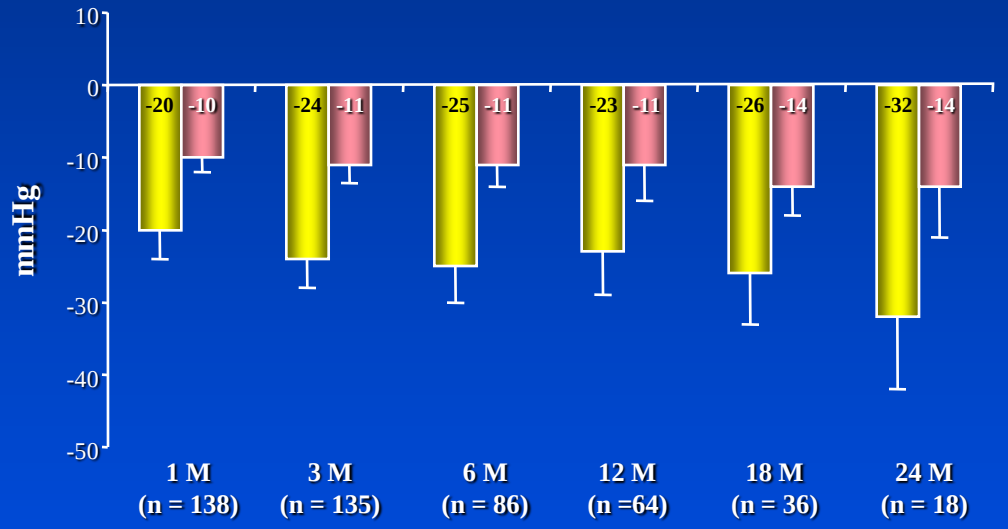
- Standard interventional technique
- 4-6 two-minute treatments per artery
- Proprietary RF Generator
  - Automated
  - Low-power
  - Built-in safety algorithms



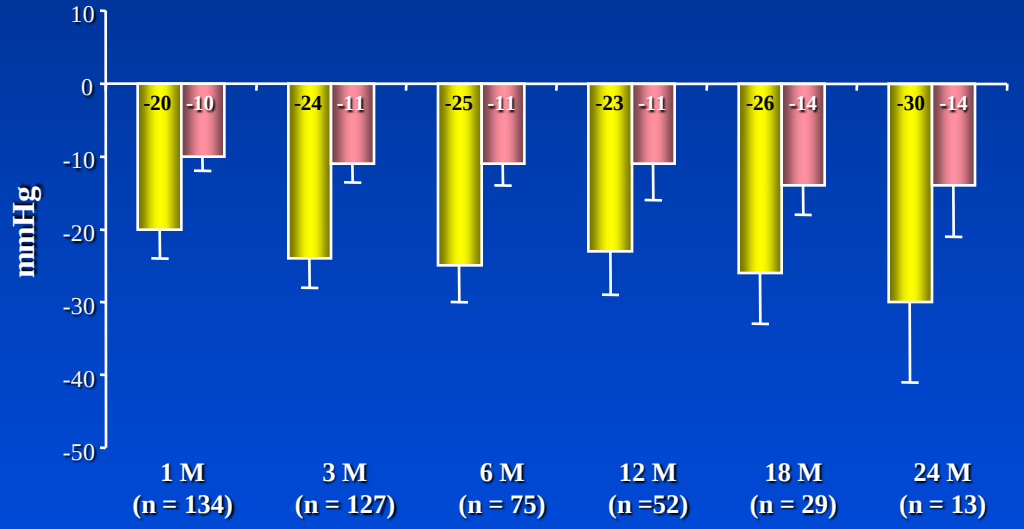
In the United States: Caution: Investigational Device. Limited by U.S. law to investigational use.

SBP and DBP changes after RD with and without censoring for medication increases post-RD

Without censoring



With censoring



Systolic
Diastolic

2466 Mo

Symplicity HTN-1 Trial Investigators, Hypertension 2011; 57: 911-917

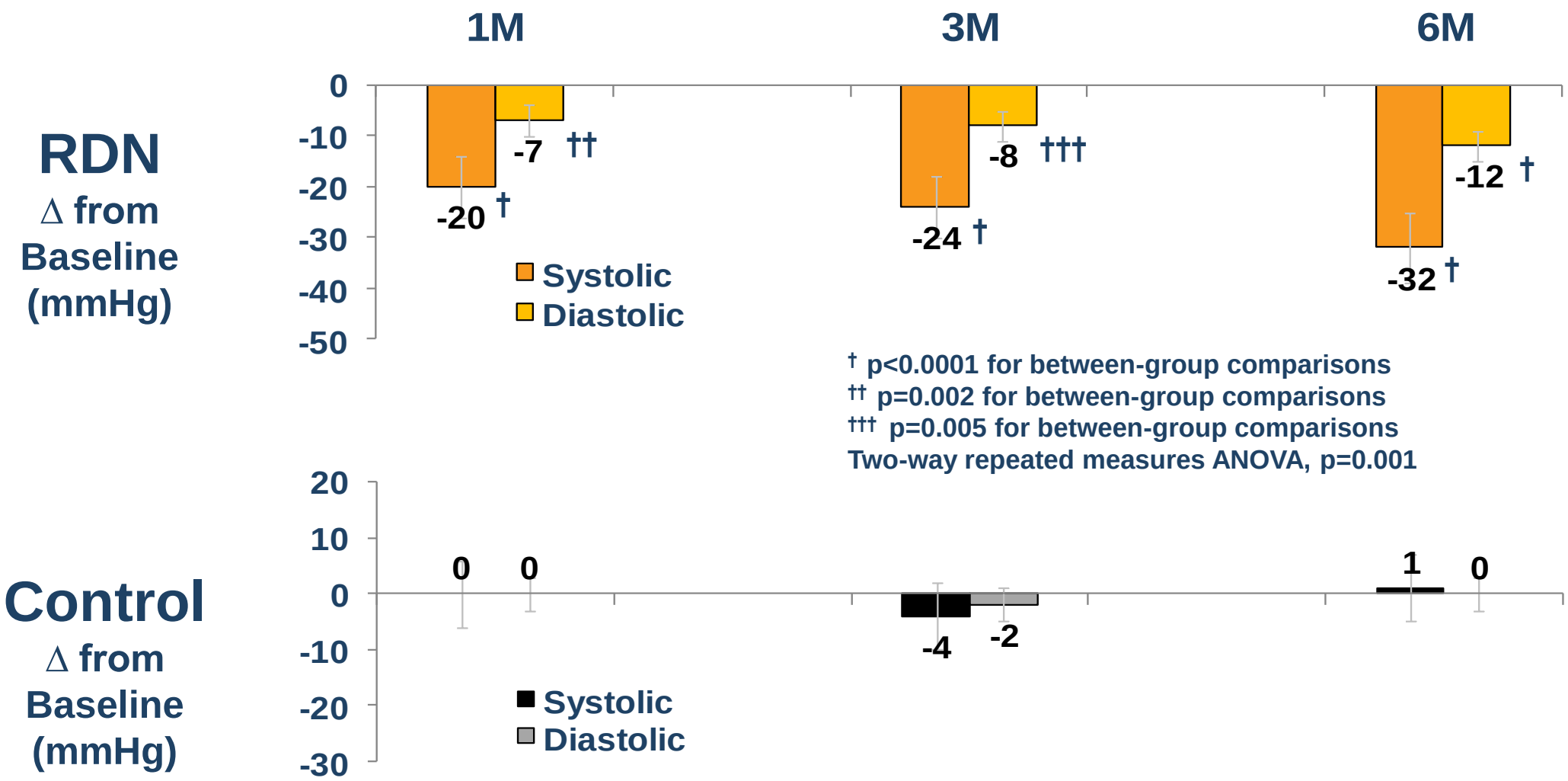
Side effects of RD in Simplicity HTN-1 Trial

- 97% of cases without complication
- 1 case of renal artery dissection
- 1 case of progression of renal artery stenosis
- No cases of orthostatic hypotension
- 3 cases of transient flank pain

Data from 153 patients with resistant hypertension, follow-up 24 months

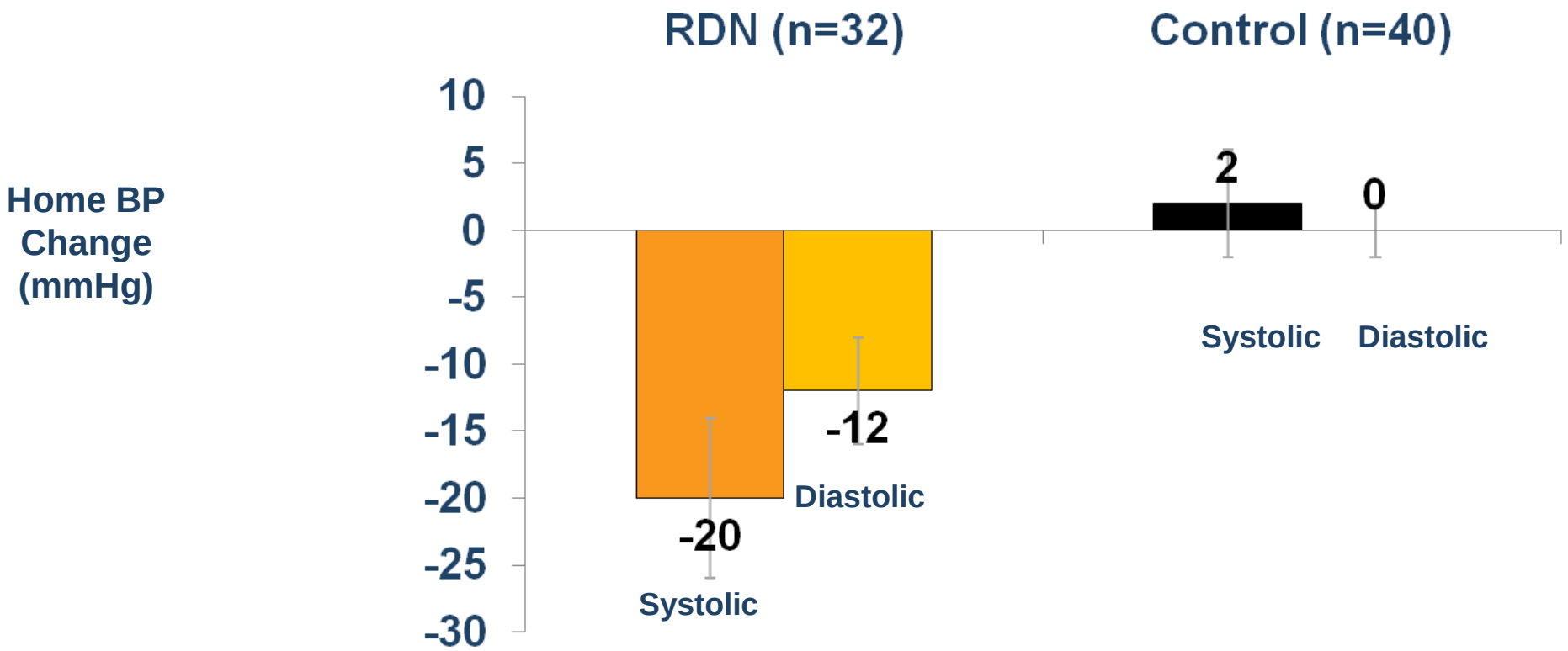
Symplicity HTN-1 Trial Investigators, Hypertension 2011; 57: 911-917

Time Course of Office BP Change



Symplicity HTN-2 Investigators. The Lancet. 2010.

Home & 24 Hour Ambulatory BP

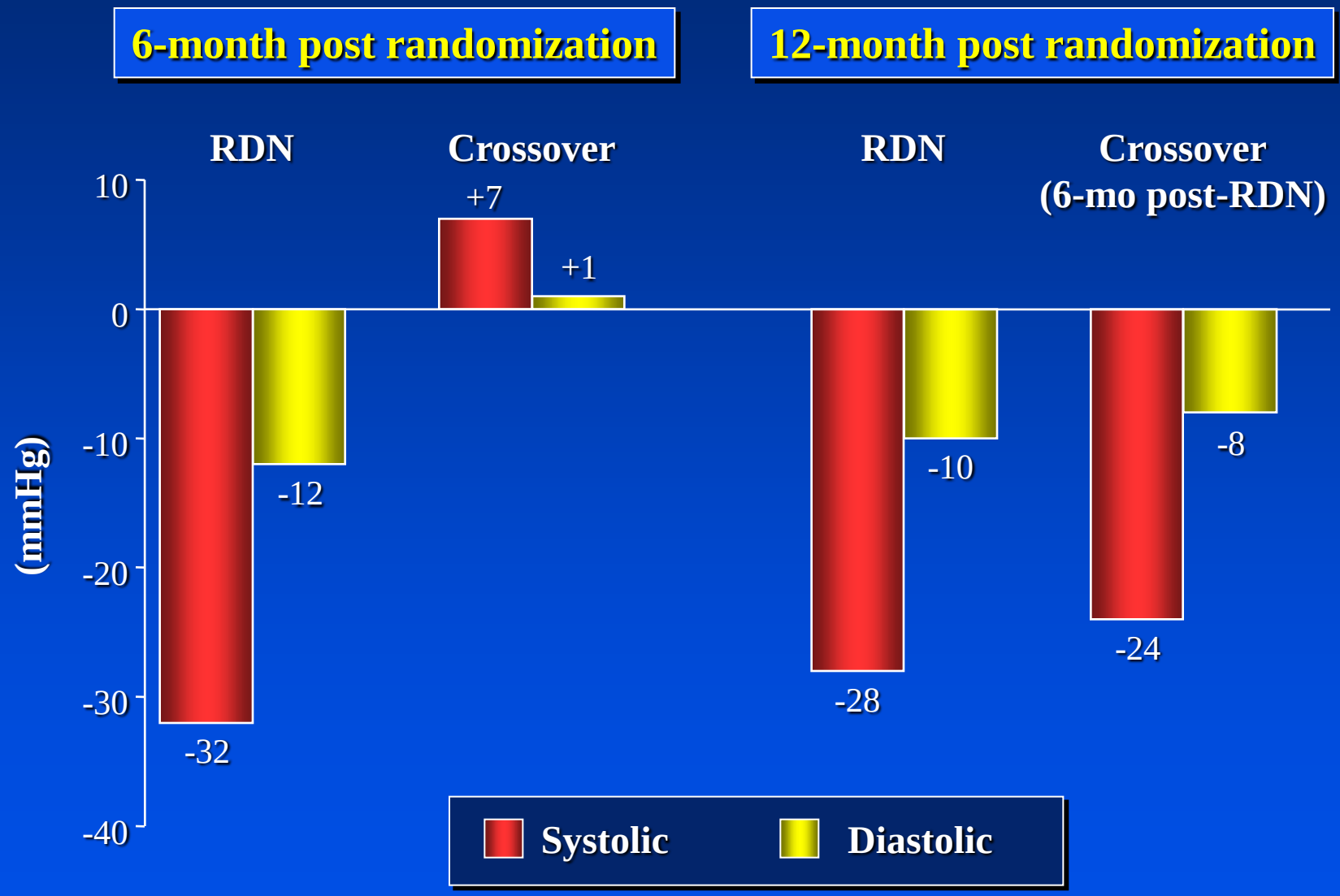


24-h ABPM:

- Analysis on technically sufficient (>70% of readings) paired baseline and 6-month
- RDN (n=20): -11/-7 mmHg (SD 15/11; p=0.006 SBP change, p=0.014 for DBP change)
- Control (n=25): -3/ -1 mmHg (SD 19/12; p=0.51 for systolic, p=0.75 for diastolic)

Symplicity HTN-2 Investigators. The Lancet. 2010.

Symplicity HTN-2 Trial: Effects of Renal Denervation on Clinical Blood Pressure in Patients with Resistant Hypertension



2761 Mo

Esler MD et al., Circulation 2012; 126: 2976-2982

Flow-chart terapia antipertensiva

- Considerare la terapia di combinazione come primo step di trattamento
- Associare classi di farmaci con meccanismi d'azione complementari minimizzando gli effetti collaterali
- Tripla terapia con diuretico, calcio-antagonista e antagonista del RAS (ACEI, ARB, DRI)
- Considerare forme secondarie di ipertensione arteriosa
- Aggiungere antialdosteronico (spironolattone, canrenoato di potassio, eplerenone)
- Considerare denervazione renale